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13. ABSTRACT (Maximum 200 Words)

The focus of this research effort is to investigate the synthesis strategies of magnetic nano-materials potentially exhibiting the temperature self-regulating properties that could be attractive for cancer therapeutic purposes. Ni-Pt alloy nano-particles are of specific interest in this study. The wet chemical approach was used (an inverse micelle method). Although micron-size particles can readily be produced with the required magnetic properties, a problem was encountered with the nano-material. Our understanding is that some surface oxidation occurs during synthesis. Attempts to modify the processing technology by employing hydrazine monohydrate as a reduction agent component yielded magnetic material suitable for further physical studies. This characterization work is now underway.

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INTRODUCTION

Hyperthermia therapy for effective cancer treatment requires maintaining the affected tissue/organ at a uniform elevated temperature, ~ 43°C for extended periods (~ 3 hours). Magnetic fluid hyperthermia is a promising recent concept for curing breast cancer. The technique also requires an advanced technical system for achieving and sustaining a uniform temperature distribution in affected tissue. Our work is focused towards achieving this specific goal. We propose to synthesize specially designed magnetic fluids with inherent thermal regulating properties. This can be accomplished by selecting magnetic alloys with the specific Curie temperature required for hyperthermia treatment (42-45 °C). When exposed to electromagnetic radiation, the magnetic particles will produce heat and eventually reach the Curie temperature, at which temperature they lose their magnetic properties, thereby terminating the heating process. We plan to extensively test and quantify the efficacy of the technique in a novel tissue model and devise protocols from the measured data. The use of thermo-regulating magnetic fluid technology together with magnetic targeting can lead to a noninvasive means of thermally destroying malignant tumors in the breast without harming the healthy surrounding tissue. This method is potentially useful for both early and advanced stages of breast cancer. This will be a versatile tool in the efficient treatment of breast cancer. The proposed research is focused on methods of fabrication, characterization, parameters optimization, and proof of concept measurements of thermo-regulating magnetic fluids.

BODY

Research activities of the first year were focused on the synthesis of the Ni-Pd nano-particles. Also, the design and construction of test measurement setups for the excitation (AC) magnetic field as well as a matched index of refraction flow loop were completed.

Task 1 SYNTHESIS OF FERROMAGNETIC Ni-Pt NANOALLOY

The complete reduction of Ni salts to form metal clusters by wet chemical methods using common reducing agents is difficult. Therefore, the reduction process was carried out using intermediary noble metals such as Pt or Pd. Reduction of compounds of the noble metals by reducing agents generates atomic species, which act as the reducing agent.

In the present case of Ni-Pt alloy, as soon as Pt atom is formed its redox potential reaches more negative potential than that of $Ni(OH)_2$ / Ni system ($E^0 = -0.72$ V) and as a result Ni^{2+} ions get adsorbed on Pt(0) and simultaneously gets reduced to Ni(0). This process proceeds autocatalytically to generate the alloy.

Two different reducing agents were employed:

1) Using $NaBH_4$: Aqueous solutions of Pt and Ni salt were prepared . They were mixed in different ratios and stirred for several hours at room temperature. After the salts were reduced with $NaBH_4$ the resulting material was washed with deionized water and dried by freeze- drying. XRD(Fig 1) and SEM(Fig 2) analyses were carried out which showed the formation of nanosized Ni-Pt alloys.

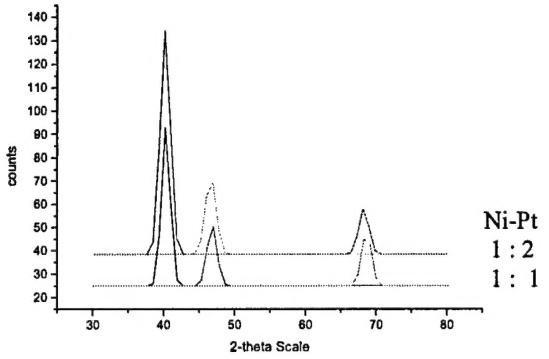

Fig 1. XRD patterns for Ni-Pt nanoalloy

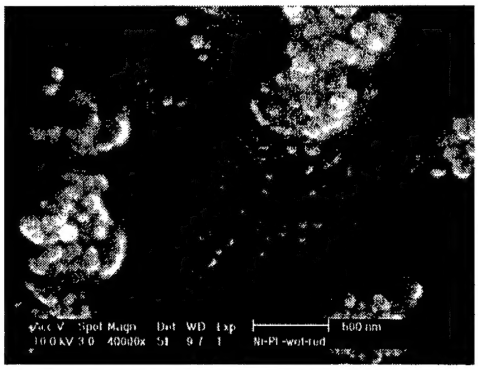

Fig 2. SEM for Ni-Pt (1:2) nanoalloy

Magnetic measurements were carried out for these samples, which showed that they are paramagnetic(Fig 3).

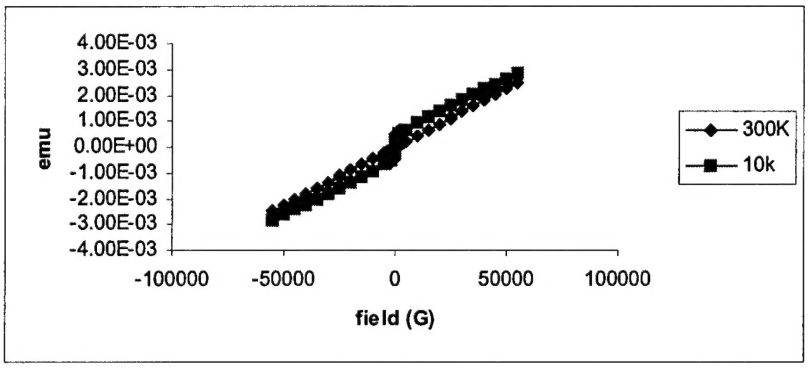

Fig 3. Hysteresis loop at 10K and 300K for Ni-Pt nanoalloy.

2) Using Hydrazine Monohydrate: The reaction was performed in a micellar CTAB medium (to stabilize the alloyed nanoparticles) of concentrations of 0.25M, 0.1M,10^{-3}M and 10^{-4} M under N_2 atmosphere. At first, Ni-salt and H_2PtCl_6 were dispersed in CTAB micellar medium. The solution was degassed by N_2 for 15min under stirring, then 30μ L of hydrazine monohydrate ($N_2H_4.H_2O$), and 200μ L of KOH solution (9.0M), were injected into the reaction mixture under stirring condition. The sample was washed, centrifuged and freeze dried. Magnetic measurement showed that these samples were superparamagnetic at room temperature (Fig 4 and 5).

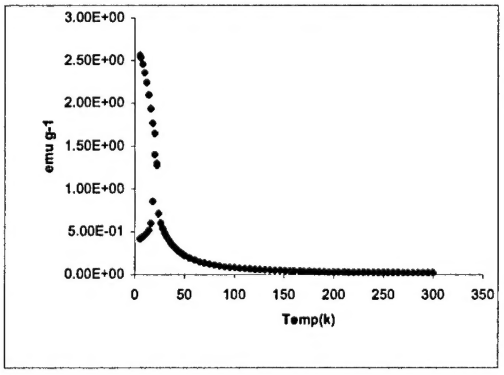

Fig 4. FC and ZFC curves for Ni-Pt (CTAB= 0.1M)

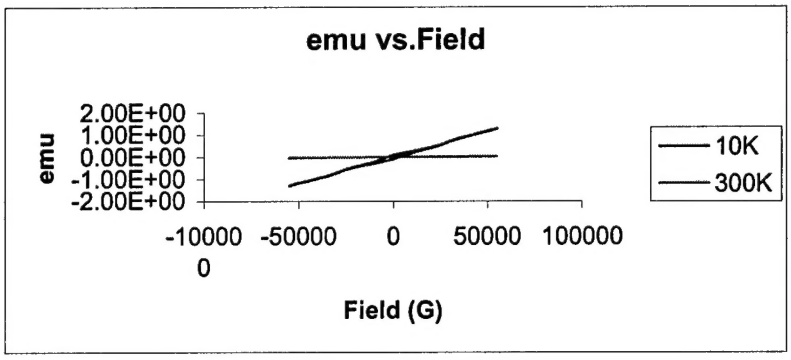

Fig 5. Hysteresis loop at 10K and 300K for Ni-Pt(CTAB=0.1 M) nanoalloy.

In order to develop magnetism in the above Ni-Pt sample, (CTAB=0.1 M), it was heated to 700^0 C for 12 hours. The sample was found to be magnetic. Then we carried out magnetic measurements (Fig6 and 7), which showed that it is still superparamagnetic at room temperature.

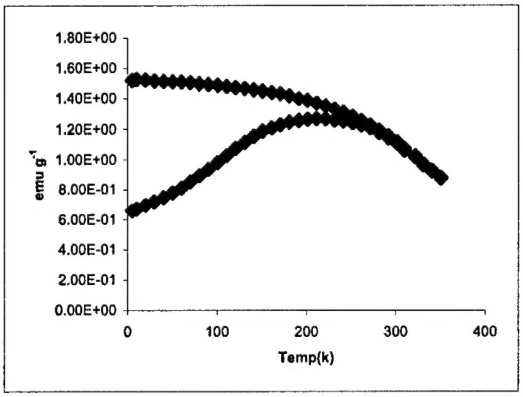

Fig 6. FC and ZFC curves for Ni-Pt (CTAB= 0.1M) after heating at 700^0C.

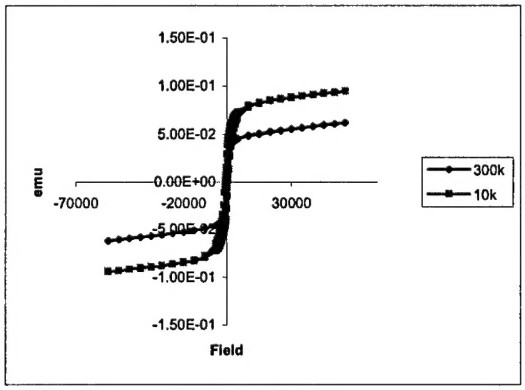

Fig 7. Hysteresis loop at 10K and 300K for Ni-Pt(CTAB=0.1 M) nanoalloy, after heating at 700^0C.

Several initial attempts to produce a ferromagnetic nano-material were unsuccessful. Our understanding is that the excessive oxidation of the nano-material occurred. Note, that larger size magnetic particles (few micrometer in diameter) could be fabricated with this route. As explained before, we selected a different method. Recent samples have quite encouraging characteristics. Although the desired value for magnetization could be higher, it is comparable to the numbers reported in the available literature. We expect to optimize the synthesis of nano-Pt-Ni material in a short time now.

Task 4 a) and b)

The matched index of refraction flow loop has been designed, fabricated and tested. It consists of the peristaltic pump, temperature controller, and a cell with acrylic beads. The Fig. 8 shows the setup. A Peltier element temperature controller is used to maintain the matched index fluid (proprietary composition from Cargille labs, NJ) at a set temperature at which the fluid matches the refractive index of the cast acrylic beads

(n=1.491). Fig. 9a demonstrates this refraction index matching using a laser beam passing through a container with acrylic beads and partially filled with the index matching fluid. Very little scattering of the laser light occurs when it passes through the beads in the fluid (Fig. 9a), whereas Fig 9b shows excessive light scattering when it passes through the beads above the fluid level.

The AC magnetic field setup has also been assembled and is functioning well. It has been used for measurements in a published on the work (Appendix 1). Fig.10 shows the setup using a 5 kW Lepel inductive heater unit.

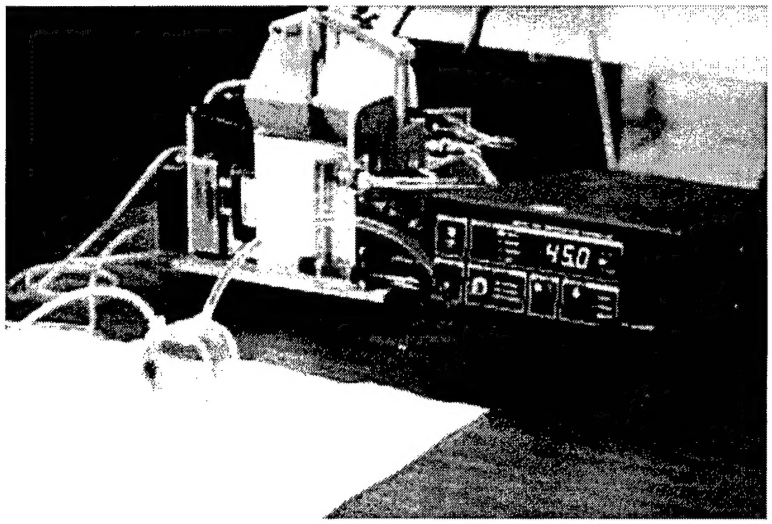

Fig. 8. The matched index of refraction flow loop setup.

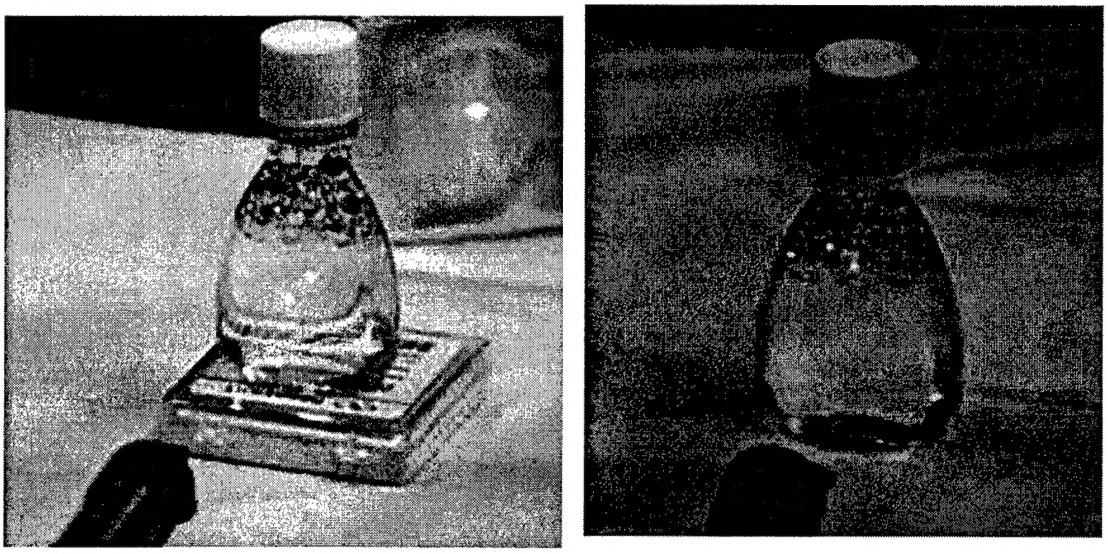

Fig. 9. a) left: Laser beam passes through the water+beads without scattering; b) right: Laser light is being blocked by the beads.

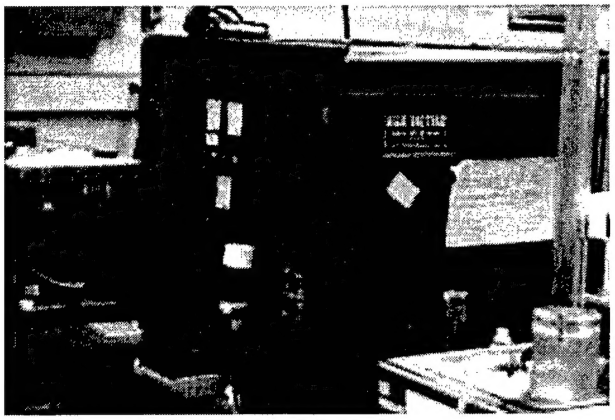

Fig.10. Radio frequency power system for magnetic fluid heating measurements.

KEY RESEARCH ACCOMPLISHMENTS

The Ni-Pt nano-material is being reproducibly synthesized with the close to the expected physical properties. Two international presentations have been made and one research paper published.

REPORTABLE OUTCOME

At this point we could report two conference presentations and one peer-rewieved proceedings paper:

1. Magnetic Microspheres and Tissue Model Studies for Therapeutical Applications, N. Ramachandran, and K. Mazuruk, presented at the *Conference on Microgravity transport processes in fluid, thermal, biological and materials Sciences Conference III, Davos, Switzerland,* Sept. 2003. Paper accepted for Conference proceedings being published by Annals of the New York Academy of Sciences, 2004.

2. Biomaterials and Magnetic fields for Cancer Therapy, by N. Ramachandran, K. Mazuruk. Presented at the *Conference on Space Technologies, Nov. 4-6, 2003, Colorado Springs, Colorado.* Conference proceedings released on CD-Rom, 2004.

CONCLUSIONS

We have found recently the synthesis route that leads to the nano-material suitable for further investigation. All the research setups are operational now and the measurements of the properties of the synthesized material are under way. We do not need to change the original work plan, as the research proceeds well and according to the proposed frame.

APPENDICES

1. paper published in the Annals of the New York Academy of Sciences.

Proceedings of the Microgravity Transport Processes in Fluid, Thermal, Biological and Materials Sciences III
Davos, Switzerland.
September 14 to 19, 2003

ECI: MTP-03-37

MAGNETIC MICROSPHERES AND TISSUE MODEL STUDIES FOR THERAPEUTICAL APPLICATIONS

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ABSTRACT

The use of magnetic fluids and magnetic particles in combinatorial hyperthermia therapy for cancer treatment is reviewed. The investigation approach adopted for producing thermoregulating particles and tissue model studies for studying particle retention and heating characteristics is discussed

INTRODUCTION

Hyperthermia is a well known cancer therapy and consists of heating a tumor region to elevated temperatures in the range of 40-46°C for an extended period of time (2-8 hours). This leads to thermal inactivation of cell regulatory and growth processes with resulting widespread necrosis, carbonization and coagulation. Moreover, heat boosts the tumor response to other treatments such as radiation, chemotherapy or immunotherapy. Of particular importance is careful control of generated heat in the treated region and keeping it localized. Higher heating, to about 56°C can lead to tissue thermo-ablation. With accurate temperature control, hyperthermia has the advantage of having minimal side effects. Several heating techniques are utilized for this purpose, such as whole body hyperthermia, radio-frequency (RF) hyperthermia, ultrasound technique, inductive microwave antenna hyperthermia, inductive needles (thermo-seeds), and Magnetic Fluid Hyperthermia (MFH). MFH offers a unique targeting capability of magnetic particles in affected tissue through the use of magnetic fields. However, this technology still suffers significant inefficiencies due to lack of thermal control.

This paper provides a review of the topic and outlines ongoing work in this area at NASA Marshall Space Flight Center (MSFC). The main emphasis is in devising ways to overcome the technical difficulty in hyperthermia therapy of achieving a uniform therapeutic temperature over the required region of the body and holding it steady for an extended period. The shortcomings stem from the non-uniform thermal properties of tissue and the point heating characteristics of the presently utilized techniques without any thermal control. Our approach is to develop a novel class of magnetic fluids, which have inherent thermoregulating properties. We have identified a few magnetic alloys which can serve as suitable nano to micron-size particle material. The objective of the investigation is to synthesize, characterize and evaluate the efficacy of Thermo Regulating Magnetic Fluids (TRMF) for hyperthermia therapy. The development of a tissue model and testing the fluid dynamics of particle motion, settling, distribution in the tissue matrix and heat generation are some of the other areas germane to this interdisciplinary project.

MAGNETIC FLUID HYPERTHERMIA RESEARCH

Hyperthermia therapy essentially consists of heating the affected regions of the body to temperatures between 40°C and 46°C that leads to the thermal inactivation of cell regulatory

and growth processes. Further, heat-treated cancer cells, in some cases, are recognized as foreign by the immune system and subsequently inactivated. For some types of cancer, hyperthermia therapy combined with the radiation- or chemo-therapy has been found to be more efficacious. Several heating techniques are utilized for this purpose, such as whole body hyperthermia, radio-frequency (RF) hyperthermia, inductive microwave antenna hyperthermia, inductive needles (thermo-seeds), and magnetic fluid hyperthermia (MFH). The latter approach is part of the general field of magnetic fluid technology, which includes techniques such as enhancement of magnetic resonance imaging, particle separation, blood cell separation, protein purification, etc., [1]. Of particular importance is the careful control of the generated heat in the treated region and keeping it localized. Higher heating, to about 56°C can lead to tissue thermo-ablation with attendant widespread necrosis, carbonization and coagulation [2].

The use of magnetic particles for hyperthermia in conjunction with alternating current (AC) magnetic fields dates back to the pioneering work of Gilchrist et al. in 1957 [3]. MFH utilizes fine micrometer size magnetic particles exposed to an alternating magnetic field. Typical field strengths are of the order of 5 – 30 kA/m with a frequency range of 100 to 500 kHz. The initial experiments resulted in a flurry of activity with the promise of realizing a powerful technique for cancer treatment. During the following decades, in-vivo experiments with animals confirmed the general applicability off the technique to human patients. However, most of the studies were conducted with inadequate animal systems, inexact thermometry and poor AC magnetic field parameters. These were the primary reasons why MFH cancer treatment has not achieved the state of clinical application till now. Renewed interest in this area stemmed from the work of Chan et al. [4] and Jordan et al. [5] who showed that on a volume basis, nanometer size magnetic particles provide more heating power and more homogeneous heating than micron-size particles. Significantly lower AC fields, more tolerable to humans, can then be used. Typically AC fields with frequencies in the MHz range lead to muscle stimulation and high field strengths lead to dangerous point heating in tissue. Another factor in favor of the technique is the availability of new biological data on heat response of cells and tissues. The first prototype of a clinical MFH therapy system has just recently come on line [6]. Set up in the Clinic of Radiation Oncology in Berlin, the system operates at 100 kHz with the field strength from 0 to 15 kA/m and with a vertical aperture of 30 – 45 cm. The treatment of deep-seated tumors especially in shielded areas such as the pelvic region and the skull still remains a challenge.

In hyperthermia therapy, magnetic particles can be introduced into the target regions inside the human body in different ways and once located, can be excited or activated to act as localized heat sources. The particles can be directly injected at the target site if possible, the most direct approach, or alternately they can be introduced into an artery by inoculation and targeting can be achieved at the desired site using a static magnetic field. It is to be noted that the magnetic targeting technique is practically realizable only for larger particles, > 1.0 μm. Recently, a new and promising technique has been demonstrated wherein 10 nm size magnetic particles in dispersion (ferrofluids) have been shown to possess highly selective cellular adhesion to tumor cells. A tenfold particle uptake by tumor cells in comparison to normal cells was reported [6]. Hence, tumor cells can be selectively loaded with magnetic particles and subsequently killed with an AC field. The particular attraction of this method is its potential to reach body target sites such as brain tumors, generally inaccessible by other techniques and the increased heat production capacity of the smaller particles. This fascinating idea may soon become an effective weapon against certain types of cancer.

There still remain serious problems with MFH that need to be understood and solved. Especially, the temperature distribution inside and outside the target region must be known precisely as a function of the AC magnetic field exposure time in order to provide optimum therapeutic temperature and to avoid overheating and damaging surrounding normal tissue. Here mathematical modeling is indispensable. Very few mathematical simulations of magnetic fluid hyperthermia has been performed so far. A one-dimensional spherically symmetric time dependent thermal model was proposed and solved analytically by Andra et al. [7]. The results were compared with data from experiments studying RF heating of a cylindrical composite. Despite the obvious difference in geometry, close agreement was reported. Other published hyperthermia modeling attempts include ultrasound, capacitive radio frequency, and ferromagnetic implant techniques. All of these simulations involve simple mathematical modeling of heat generation and do not account for the effects of blood perfusion that is always present in the tumor area; Tomkins et al., [8].

Ongoing research is focused on specific issues relating to the optimization of the magnetic fluid properties. For example, for a given excitation frequency, a sharp particle size distribution is required in order to maximize the Specific Absorption Rate (SAR) given in terms of Watts/gm. Further optimization may involve properties of the particle coating. For colloidal stabilization, a magnetic particle has to be coated with a surfactant layer. The interaction of this colloidal shell with the core of the particle in an AC magnetic field can be very complex. For example, the core can exhibit oscillations within the shell, or, alternatively, the whole particle can oscillate depending on elastic properties of the shell. Detailed study is required to describe particle oscillations in AC magnetic fields. Also the role of hydrodynamic and rheological properties of the solvent is of importance. Selection of appropriate surfactants used for the particle shells is also of great importance as selective cellular adhesion can potentially be achieved. This is

especially vital since targeting of nanometer size particles by an exterior magnetic field is not very practical. Brownian motion keeps the particles suspended, even in strong magnetic fields, and in the presence of system flow the particles are transported with the flow.

Other approaches to cancer therapy using magnetic particles include reducing the blood circulation in the tumor area by overloading it with magnetic particles and thereby embolyzing it [9], and overloading the tumor cell itself (uptake mechanism discussed earlier) leading to arrest of the cell division and to subsequent lyses [10]. Magnetic microspheres as drug carriers alone is another attractive research field overlapping hyperthermia. Clearly the focus now is on the search for novel biocompatible ferrofluids with better SAR and precise cancer cell targeting selectivity.

An excellent overview of the applications of MMS and magnetic fluids in cancer therapy can be found in the book edited by Häfeli et al. [11].

REQUIREMENTS AND SPECIFICATIONS FOR MFH APPLICATIONS

The technical and medical requirements for hyperthermia application systems are rather advanced and difficult to fulfill. From a practical standpoint, the AC magnetic field homogeneity and its control, safety, accurate thermometry, and a precisely delineated treatment volume are the primary parameters that have to be met. This is a complex problem that requires advanced thermal modeling complemented with experimental work. In order to make this presentation more complete, specific issues such as particle size, toxicity, dissipation processes and macroscopic heat and mass transport are briefly discussed.

Particle Synthesis

In general, ferrofluids consist of three components: carrier, surfactant, and magnetic particles. The most important component responsible for its many unusual properties is obviously the dispersed nanoparticle phase. A variety of techniques have been developed in the past to obtain these nanoparticles, which can be based on either chemical or physical processes. Physical methods have a higher yield in general, but chemical methods are more versatile and practical especially for a research laboratory environment. Examples of the methods are: vacuum evaporation, electrolytic precipitation, chemical vapor deposition, spark erosion, wet chemical methods, and aerosol methods. Rosensweig [12] has written an excellent treatise on ferrofluids, their synthesis techniques and properties, as well as theoretical concepts dealing with their transport and behavior in magnetic fields. Many of the abovementioned methods suffer from a lack of control of the particle size distribution. Particle synthesis can be approached in a number of ways. We focus on a couple of tried and promising wet chemistry techniques such as microemulsion based approaches. The microemulsion approach is a reverse-micelle technique that gives a good narrow size distribution and is being successfully used in many laboratories for the synthesis of particles, for example Zeolites [13]. These water-in oil micro-emulsions form a system of so called reverse micelles, which act as micro-reactors. The size of these minute water pools influences the size of the synthesized micro-crystals to some extent. Size control is then accomplished by a simple variation of the molar ratio water/surfactant or water/oil in the system. Hori et al.[14] and Nonumara et al.[15] have recently prepared Pd/Ni alloy nanoparticles by wet chemistry.

Particle size and type

Particles stabilized by biocompatible substances must have appropriate shapes and sizes – below a few micro-meters, in order to pass through the capillary system without posing a threat of vessel embolism or physical irritation of the surrounding tissue. We focus on two categories, namely, magnetic fluids and magnetic microspheres, each with very specific chemical and physical characteristics.

Magnetic fluids are comprised of 1 – 100 nm magnetic particles (magnetite, iron, nickel, etc.) freely dispersed in a carrier fluid. Due to their small dimensions, Brownian thermal molecular motion keeps them suspended and prevents sedimentation in gravitational or magnetic fields. A continuum fluid model has been shown to work well to describe these magnetic fluids [12]. The particles have to be usually coated with a surfactant (such as oleic acid or a biocompatible substance) or stabilizing polymer layer to prevent aggregation. This layer also provides the unique chemistry driven surface adhesion properties of these particles to tissue. As a result, the particles in magnetic fluids interact with each other by means of magnetic dipoles, stearic or electrostatic repulsion, and hydrodynamic forces. The thickness of stabilizing layers is usually of the order of 2-3 nm, so that the hydrodynamic size of the particles can be different from the magnetic core.

Magnetic Microspheres (MMS) are magnetic particles in the 0.1 -100 μm size range, and have stronger dipole-dipole interactions than the thermal fluctuation energy. The particles can be used without coatings (such as iron particles with carbon) or specifically tailored for function by applying polymer, silan or dextran type coatings. In strong magnetic fields, these particles form rigid spatial structures that can be utilized for selectively occluding blood vessels or for targeting them in a specific organ and retaining them there for extended periods (days).

Toxicity

Magnetic fluid particles for in vivo applications have to be biocompatible, preferably biodegradable and non-toxic. These criteria rule out many attractive magnetic materials from consideration. Toxicity studies of various types of commercially available microspheres such as magnetic and

non-magnetic polylactic acid microspheres, FeC, dextran-coated magnetite nanospheres, magnetic polystyrene nanospheres, etc. have shown no significant difference in viability, Häfeli et al. [16]. The amount of material needed for magnetically targeted therapy is only a few milligrams. This is significantly lower than the lethal iron dosage of 200 mg of iron per kg of human body. At lethal levels they can cause acidosis of the body or induce thrombosis of the lung's vascular systems [17]. In summary, iron- and iron-oxide based particles show no adverse effects to humans or animals in small quantities.

Power dissipation

The measure of AC power dissipation in ferrofluids is the Specific Absorption Rate (in Watts per gram of fluid) or alternatively, the complex magnetic susceptibility of the ferrofluid. Only a few experimental reports on measurement of the magnetic susceptibility as a function of frequency are available in surveyed literature [18]. There is a significant body of work dealing with the theoretical development of the fundamentals of ferrofluids and its properties and these can be used to gain insight into microscopic processes responsible for the heating of ferrofluids when subjected to dynamic magnetic fields. Solving the equations governing the dynamics of the magnetic moment of a particle (Langevin approach) results in particle relaxation times. This when used in conjunction with Debye theory yields the required susceptibility [19].

HEAT GENERATION

Two rotational relaxation mechanisms may coexist in magnetic fluids when an AC magnetic field is imposed. In magnetic fluids that are composed of subdomain particles (nm in size), the Neel relaxation [20], when the magnetic moment moves with respect to the mechanical particle, and the Brownian relaxation corresponding to the rotation of the particle inside a fluid [21] are the main mechanisms of heat generation. The latter usually dominates the relaxation process in magnetic fluids. As the particles get larger, multidomain particles (microns in size), hysteresis loss is the main mechanism of heat generation [2]. The SAR of magnetic fluids is proportional to H^2, where H is the magnetic field strength and for larger particles, the heat production is proportional to H^3 [21].

The modeling of heat production from magnetic particles from fundamentals is rather complex that involve the momentum conservation equation for the flow field, the magnetostatic equations and a constitutive equation for the particle magnetization [19]. Our approach is to use the heat generation data from experiments in the numerical model to study its transport and diffusion when subjected to a flow field. This approach will provide a benchmarked predictive numerical model that can be used for the simulation of hyperthermia protocols for known system flows using known particle behavior and for dialed in values of the magnetic excitation field.

SYNTHESIS OF THERMOREGULATING PARTICLES

There are a couple of promising wet chemistry recipes for the development of magnetic particles, typically in the 1-10 nm range. There also exist several candidate alloying metals that can give us the attributes required of such particles, namely, a fairly low Curie temperature (40 to 60 °C), a large magnetic moment, and biocompatibility. Here we describe the reverse micelle or microemulsion technique for synthesizing particles. The microemulsion approach is a reverse-micelle technique that gives a good narrow size distribution and is being successfully used in many laboratories for the synthesis of nanoparticles. It consists of performing chemical synthesis in tiny droplets of water encapsulated in oil – the micro reactors where nuclei germinate and grow into larger particles. This approach has been used for the synthesis of over 50 different materials [22] and has been shown to be a versatile way of producing inorganic nanoparticles. There is still considerable debate as to the exact mechanism of the formation of the particles. For a while the radius of the droplets was thought to be the constraint on the resulting particle size [23] but experiments have yielded particles larger than the droplets of the microemulsion used [24]. The current thinking is a modification of the mechanism first proposed by LaMer [25] and holds that the particle size control is dictated by the kinetics of the elementary steps of particle formation [24].

The microemulsions are mixtures of three components, water, oil, and surfactant. On the oil-rich side, a water-oil microemulsion consists of water droplets in the continuous oil phase with the water and oil domains separated by a film of self-assembled surfactant molecules. They can be easily prepared by mixing water, oil (such as cyclohexane) and surfactant in a glass tube and then heating to an appropriate temperature. The microemulsion is formed spontaneously by gentle shaking. The radius of the micelles can be controlled by the water to oil ratio, or by the surfactant percentage and can vary from a few nanometers to microns. As an example consider the synthesis of palladium nanoparticles [26]. Palladium chloride microemulsion is formed using 75 wt.% of cyclohexane (oil phase), 20 wt.% of Marlipal O13/40 surfactant, and 5 wt.% of aqueous solution of the reactants. A typical water droplet size of 1.7 nm is obtained. The two aqueous solutions (reactants) used in the process contain 0.2 mol/l $PdCl_2$.NaCl and 0.6 mol/l $NaH_2PO_2.H_2O$ of reducing agent, respectively. The resulting microemulsion is fed into a reactor and mixed. Fairly monodisperse palladium particles, 5.1 nm in diameter with a standard deviation of 0.5 nm are obtained. If just the reactant aqueous solutions (no emulsion) are mixed palladium particles with a rather broad size distribution in the range of 2 to 15 nm diameter, are formed.

The phase diagram for Nickel-Palladium alloy is shown Fig. 1. Also shown is the Curie temperature that can be

controlled by controlling the Nickel composition in the alloy. Other possible alloys that have a tunable Curie temperature are Ni-Zn, Ni-W, Ni-Pt, Ni-Si, Ni-Sb, Co-Pd, and Co-Mn. Additional chemistry aspects include the addition of appropriate surfactants such as oleic acid used in ferrofluid dispersions and a carrier fluid (water or oil based). Obtaining a good dispersion of the synthesized particles is no trivial task and there is a wide choice of surfactants that can be tested and utilized. Also, there is the issue of the biocompatibility of the dispersion agent. We plan to initially test surfactants that are in use for suspending commercially available MMS that are used in therapy and clinical trials. The parameters to be tested for the synthesis protocol include the particle size, agglomeration characteristics, magnetic moment and Curie temperature.

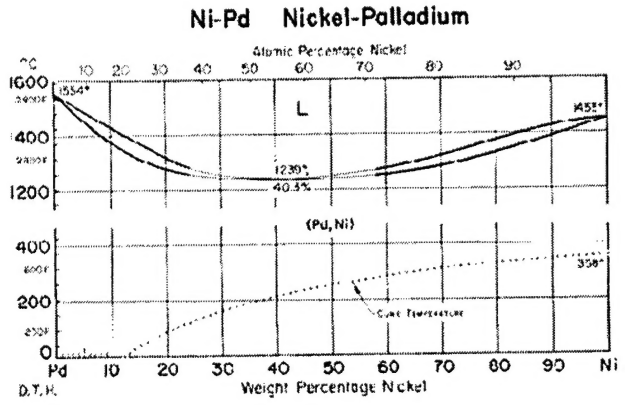

Fig. 1 Phase diagram for Nickel-Palladium alloy. Also shown is the Curie temperature that can be controlled by controlling the Nickel composition in the alloy.

In addition to the Ni-Pd alloy we will attempt to synthesize two additional alloys from the candidates identified above. These are identified in Table 1 below.

Table 1
Alloy combinations for thermoseed particle synthesis
Numbers correspond to weight % ;
Target Curie temperature ~ 50 °C

Pd (85%) – Ni (15%)
Pt (62%) – Ni (38%)
Ni (81%) – Zn (19%)

MATERIALS PROCESSING AND TISSUE MODEL EXPERIMENTS

For targeted delivery studies using a static magnetic field a fluids experiment model and associated diagnostics are required. While experiments in test tubes and capillary tubes are easily performed and will form a part of this investigation, they have a major shortcoming in that they do not simulate tissue even in the remotest sense. The length scales of tissue are in the 1-30 μm size (arterioles, venules and capillaries) and more importantly they are present as a diffuse network. Blood perfusion is an added complexity that cannot be ignored if one is to obtain meaningful and correlatable results. Fig. 2 shows a schematic of the dimensions (diameter) of different types of blood vessels along with typical values of blood flow rates in the human body. Blood can be treated as a Newtonian fluid when flowing in arteries and veins > 100 μm in diameter and a non-Newtonian model is more appropriate in smaller vessels such as capillaries. The volumetric perfusion rate, usually given in units of ml (blood)/(cm^3 tissue. min) varies from 0.02 in skeletal muscle at rest to 2.0 during heavy exercise [27]. It varies primarily in response to the oxygen demand of the body. The maximum flow Reynolds number in arteries is ~ 300 to 600 [28].

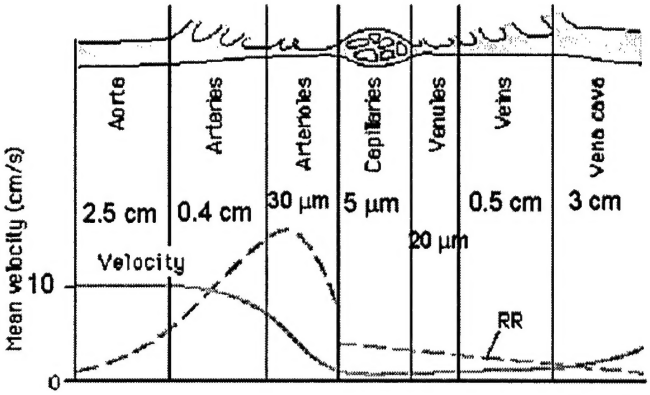

Fig. 2 Typical dimensions and blood perfusion rates in human blood vessels. RR is the relative resistance, which is highest in the arterioles.

Surveyed literature has yielded no unique way of simulating tissue and blood flow. Investigators have utilized 40% glycerol in water to essentially get the working fluid viscosity to match the blood viscosity of 3.6 cP at 37 °C but so far the perfusion framework has been limited to tubular and jagged-tubular structures with a few bifurcations to simulate the hemodynamics in major blood vessels [29-31]. On the hyperthermia front, model experiments have essentially been conducted in gels [21] to measure heat production and dissipation. For this investigation, we propose the approach of utilizing the technique of refractive index matching for the simulation of a capillary bed, system perfusion and hyperthermia studies. The technique is elaborated below.

MATCHED INDEX OF REFRACTION STUDIES

The basic premise of the technique is to match the refractive index 'n' of the experiment model (cast acrylic, n = 1.491) and the working fluid. Specially formulated fluid

mixtures and precise temperature control are used to match the refractive indices of the fluid and the model material, which essentially makes the internal geometry of the model transparent. Coupled with external flat surfaces, the experimenter can then use Laser Doppler Velocimeter (LDV), Particle Image Velocimeter (PIV) and Phase Doppler Particle Analyzer (PDPA) in order to make non-intrusive particle and flow diagnostic measurements anywhere within the model. We have done some preliminary work in this area in order to identify a working fluid suitable for lab operations [32]. Some of the considerations in the study were to identify candidate fluids (or fluid blends) for proper refractive index matching of cast acrylic (typical model material). Requirements included good operational characteristic (reasonable temperature range), non-toxic (safety), chemical stability (inertness), cost, non-corrosive (does not consume the plastic model), low viscosity (good Reynolds number, Re, range from dynamic similitude standpoint), safe (combustion hazard), ease of operation (non-volatile – not requiring a sealed system), and being colorless and odorless. Three potential fluid combinations were identified:

Table 2
Matched Index of Refraction Fluids
(n = 1.491 => cast acrylic)
n: index of refraction; ν : kinematic viscosity

1. 73% Dow Corning 550m Silicone oil and 27% Union Carbide L42 fluid ;
n = 1.491 @ 22C, ν = 188 Cst, den = 1.04 gm/cc

2. 68.2% Turpentine and 31.8% Tetraline
n = 1.491 @25C, ν =1.63 Cst, den = 0.896 gm/cc

3. Hydrocarbon liquid mixture : Cargille labs, NJ (propriety composition)
n = 1.491 @ 25C, ν = 27 Cst, den = 0.879 gm/cc

The choice of the appropriate fluid will depend on compatibility with magnetic fluids and other factors identified above.

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